

## SEARCH REQUEST FORM

Examiner # (Mandatory): 65525Requester's Full Name: John plaseArt Unit 1624 Location (Bldg/Room#): 4E15Phone (circle 305 306 308) 4714Serial Number: 09/706683

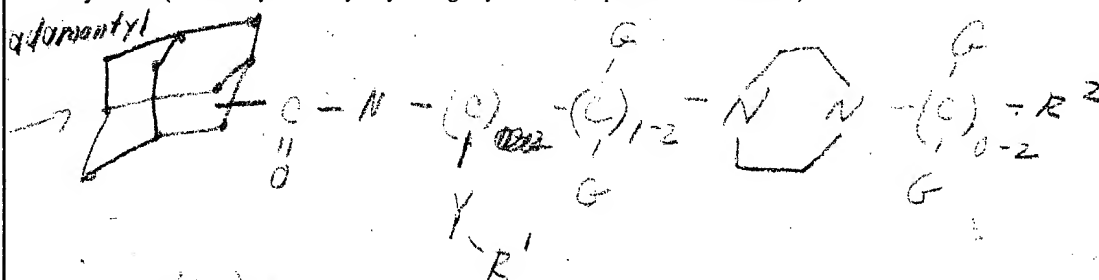
Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention \_\_\_\_\_

Inventors (please provide full names): \_\_\_\_\_

Earliest Priority Date: \_\_\_\_\_

Keywords (include any known synonyms registry numbers, explanation of initialisms):



## Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

$$\text{R}^2 = \text{phenyl or naphthyl} - \text{optionally subst.}$$

RECEIVED  
MAY - 9 2001  
(STIC)

## STAFF USE ONLY

Searcher: JOHN DANTZMAN

Type of Search

Vendors (include cost where applicable)

Searcher Phone #: \_\_\_\_\_

N.A. Sequence

☒ STN

Searcher Location: \_\_\_\_\_

A.A. Sequence

☐ Questel/OrbitDate Picked Up: 5-11-01

Structure (#)

☐ Lexis/NexisDate Completed: 5-11-01

Bibliographic

☐ WWW/InternetClerical Prep Time: 25

Litigation1

☐ In-house sequence systems (list)

Terminal Time: \_\_\_\_\_

Fulltext

☐ DialogNumber of Databases: 25

Procurement

☐ Dr. Link

Other

☐ Westlaw☐ Other (specify)

BERNHARDT

09/706683

=> d his

(FILE 'HOME' ENTERED AT 10:39:02 ON 11 MAY 2001)

FILE 'REGISTRY' ENTERED AT 10:39:10 ON 11 MAY 2001

L1 STR  
L2 0 S L1  
L3 STR L1  
L4 18 S L3  
L5 1040 S L3 FUL  
SAV L5 BERN706/A TEMP  
L6 5 S L1 FUL SSS SUB=L5

FILE 'CAPLUS' ENTERED AT 11:07:30 ON 11 MAY 2001

L7 1 S L6

CAOLD

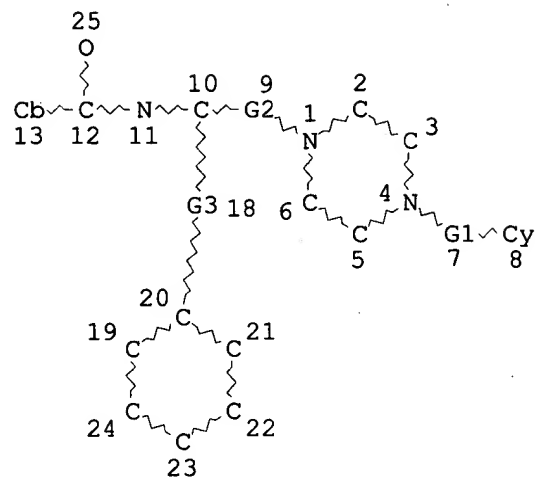
zero hits

Beulstein

zero hits

=&gt; d que 16

L1 STR



REP G1=(0-2) C

REP G2=(1-2) C

REP G3=(0-4) A

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

GGCAT IS PCY SAT AT 13

DEFAULT ECLEVEL IS LIMITED

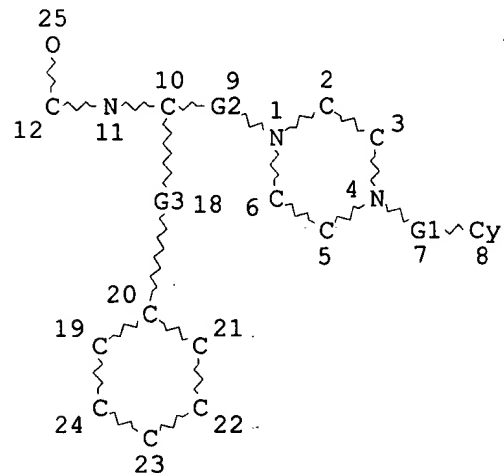
GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE

L3 STR



REP G1=(0-2) C

BERNHARDT

09/706683

REP G2=(1-2) C  
REP G3=(0-4) A  
NODE ATTRIBUTES:  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE  
L5 1040 SEA FILE=REGISTRY SSS FUL L3  
L6 5 SEA FILE=REGISTRY SUB=L5 SSS FUL L1

=> d bib abs hitstr

L7 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS

AN 1999:757952 CAPLUS

DN 132:117085

TI Synthesis and SAR of Adatanserin: Novel Adamantyl Aryl- and Heteroarylpiperazines with Dual Serotonin 5-HT1A and 5-HT2 Activity as Potential Anxiolytic and Antidepressant Agents

AU Abou-Gharbia, Magid A.; Childers, Wayne E., Jr.; Fletcher, Horace; McGaughey, Georgia; Patel, Usha; Webb, Michael B.; Yardley, John; Andree, Terrance; Boast, Carl; Kucharik, Robert J.; Marquis, Karen; Morris, Herman; Scerni, Rosemary; Moyer, John A.

CS Chemical Sciences and CNS Disorders, Wyeth-Ayerst Research, Princeton, NJ,

08543-8000, USA

SO J. Med. Chem. (1999), 42(25), 5077-5094

CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

OS CASREACT 132:117085

AB Several novel functionalized adamantyl aryl- and heteroarylpiperazine derivs. were prep'd. and exam'd. in various receptor binding and behavioral tests to det. their serotonin receptor activities. Many compds. demonstrated modest to high affinity for 5-HT1A receptors. 2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl adamantyl-1-carboxylate demonstrated relatively high affinity for 5-HT1A receptors ( $K_i = 8$  nM)

and

acceptable selectivity vs. D2 receptors ( $K_i = 708$  nM); however, it lacked in vivo activity in serotonergic behavioral models. In contrast, WY-50,324 (SEB-324, adatanserin) (adamantyl-1-carboxylic acid 2-[4-(2-pyrimidinyl)-1-piperazinyl]ethylamide) (I) and adamantyl-1-carboxylic acid 2-[4-(2-methoxyphenyl)-1-piperazinyl]ethylamide demonstrated high affinity for 5-HT1A binding

sites

( $K_i = 1$  nM for both) and moderate affinity for 5-HT2 receptors ( $K_i = 73$  and 75 nM, resp.). Both compds. also demonstrated partial 5-HT1A agonist activity in vivo in rat serotonin syndrome and 5-HT2 antagonist activity in quipazine- and DOI-induced head shake paradigms. The selective 5-HT1A partial agonist and 5-HT2 antagonist activity of I was accompanied by significant anxiolytic activity in an animal conflict model. On the

basis

of this profile, comp'd. 9 entered development as a combined anxiolytic

and

antidepressant agent.

IT 256351-85-6P 256351-86-7P 256351-87-8P

256351-88-9P 256351-89-0P

RL: BPR (Biological process); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process) (synthesis and SAR of adatanserin by prepn. of novel adamantyl and aryl- and heteroarylpiperazines with dual serotonin 5-HT1A and 5-HT2 activity as potential anxiolytic and antidepressant agents)

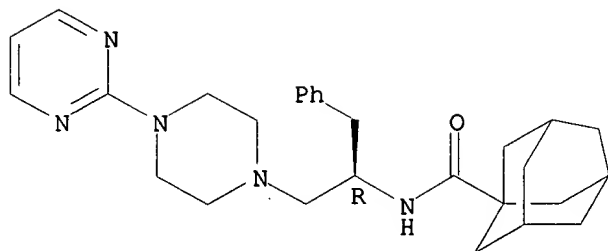
RN 256351-85-6 CAPLUS

CN Tricyclo[3.3.1.1.3,7]decane-1-carboxamide,

N-[(1R)-1-(phenylmethyl)-2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

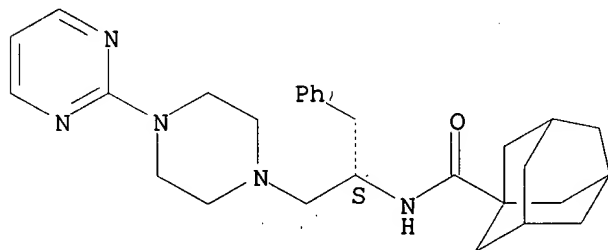
11/28/99



RN 256351-86-7 CAPLUS

CN Tricyclo[3.3.1.1.3,7]decane-1-carboxamide,  
N-[(1S)-1-(phenylmethyl)-2-[4-(2-  
pyrimidinyl)-1-piperazinyl]ethyl]- (9CI) (CA INDEX NAME)

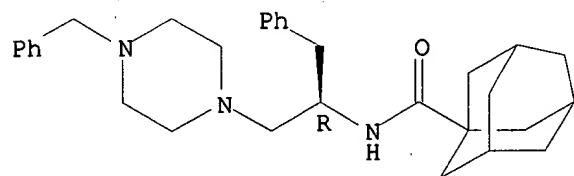
Absolute stereochemistry. Rotation (+).



RN 256351-87-8 CAPLUS

CN Tricyclo[3.3.1.1.3,7]decane-1-carboxamide, N-[(1R)-1-(phenylmethyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

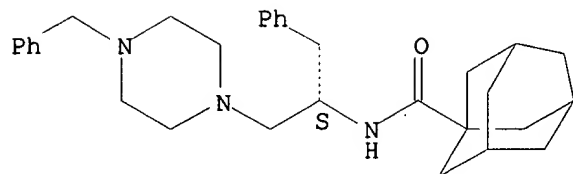


● 2 HCl

RN 256351-88-9 CAPLUS

CN Tricyclo[3.3.1.1.3,7]decane-1-carboxamide, N-[(1S)-1-(phenylmethyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-, dihydrochloride (9CI) (CA INDEX NAME)

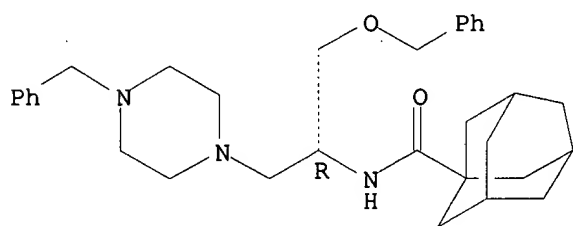
Absolute stereochemistry. Rotation (+).



● 2 HCl

RN 256351-89-0 CAPLUS  
 CN Tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-carboxamide, N-[(1R)-1-  
 [(phenylmethoxy)methyl]-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-,  
 dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



● 2 HCl

RE.CNT 85

RE

- (1) Abou-Gharbia, M; US 4797489 1989 CAPLUS
  - (4) Albinsson, A; Eur J Pharmacol 1994, V261, P285 CAPLUS
  - (6) Barrett, J; Drug Dev Res 1991, V24, P179 CAPLUS
  - (7) Barrett, J; Psychopharmacology 1993, V112, P1 CAPLUS
  - (8) Bojarski, A; Wiad Chem 1994, V48, P419 CAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

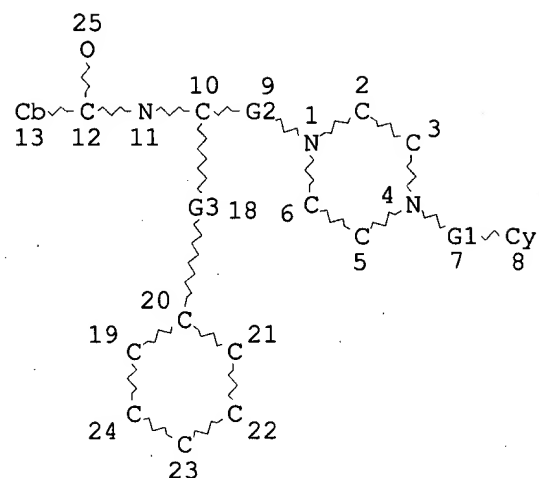
BERNHARDT

09/706683



L1

STR



REP G2=(1-2) C

NODE ATTRIBUTES:

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

GGCAT IS PCY SAT AT 13

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE

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L9          0 SEA FILE=BEILSTEIN SSS FUL L1
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=> d his

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FILE 'REGISTRY' ENTERED AT 12:54:57 ON 11 MAY 2001

L1 STR 256351-85-6  
ACT BERN706/A

L2 STR  
L3 1040 SEA FILE=REGISTRY SSS FUL L2

L4 STR L2

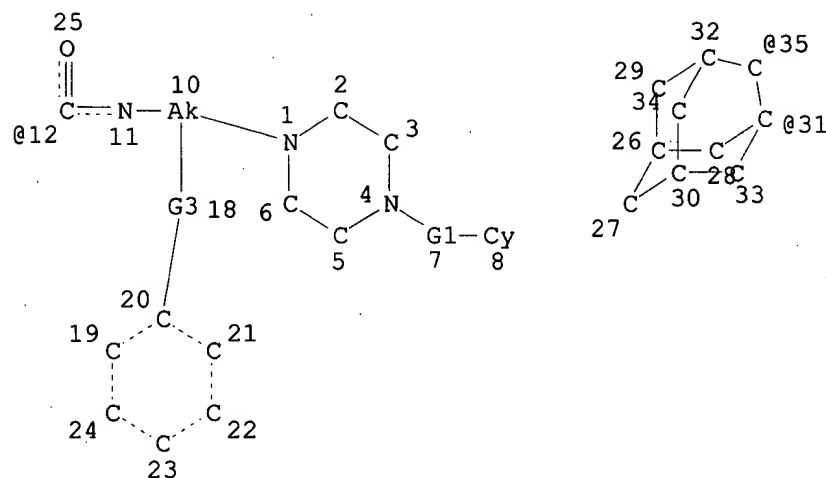
FILE 'MARPAT' ENTERED AT 12:57:57 ON 11 MAY 2001

L5 0 S L4  
L6 2 SEAR SSS SAM L4  
L7 13 SEAR SSS FUL L4  
L8 2 S L7/COMP

=&gt; d que 18

L4

STR



REP G1=(0-2) C

REP G3=(0-4) A

VPA 12-31/35 U

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:

MLEVEL IS ATOM ON RING NODES AND RING GROUPS

MLEVEL IS CLASS ON CHAIN NODES AND CHAIN GROUPS

ECLEVEL IS LIM ON ALL NODES

ALL RING(S) ARE ISOLATED

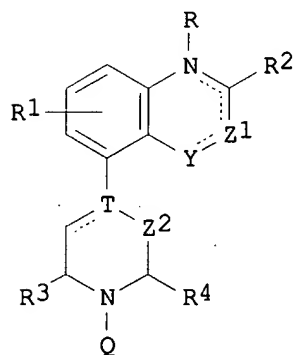
L7 13 SEA FILE=MARPAT SSS FUL L4 (MODIFIED ATTRIBUTES)

L8 2 SEA FILE=MARPAT ABB=ON PLU=ON L7/COMP

=&gt; d ibib abs fqhit 1-2

L8 ANSWER 1 OF 2 MARPAT COPYRIGHT 2001 ACS  
 ACCESSION NUMBER: 130:223299 MARPAT  
 TITLE: Preparation of 5-piperazinotetrahydroquinolines and  
 analogs as 5-HT<sub>1</sub> receptor agonists  
 INVENTOR(S): Feenstra, R. W.; Visser, G. M.; Kruse, C. G.; Tulp,  
 M.  
 T. M.; Long, S. K.  
 PATENT ASSIGNEE(S): Duphar International Research B.V, Neth.  
 SOURCE: Eur. Pat. Appl., 26 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 900792	A1	19990310	EP 1998-202832	19980824
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2246126	AA	19990302	CA 1998-2246126	19980828
JP 11147871	A2	19990602	JP 1998-259105	19980831
US 6214829	B1	20010410	US 1998-144076	19980831
PRIORITY APPLN. INFO.:			EP 1997-202704	19970902
GI				

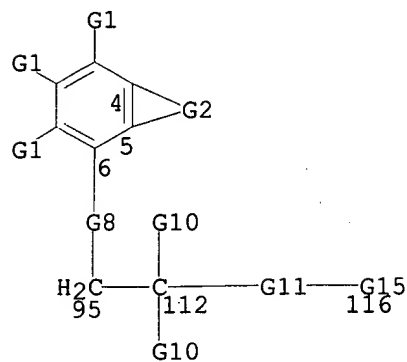


I

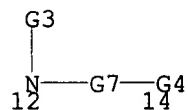
AB Title compds. [I; Q = CH<sub>2</sub>CR<sub>5</sub>R<sub>6</sub>ZR<sub>7</sub>; R, R<sub>3</sub>, R<sub>4</sub> = H or alkyl; R<sub>1</sub> = H or F; R<sub>2</sub>  
 = H, alkyl, oxo (sic); RR<sub>2</sub> = bond; R<sub>5</sub>, R<sub>6</sub> = H, alkyl, alkylphenyl; R<sub>7</sub> =  
 cyclic group (sic), (hetero)aryl, adamantyl, etc.; T = N or C (sic); Y =  
 C, O, N, or S (sic); Z = CH<sub>2</sub>O, CH<sub>2</sub>CO, NHCO, etc.; Z<sub>1</sub> = (CR'')<sub>p</sub>; R'' = H  
 or alkyl; Z<sub>2</sub> = (CH<sub>2</sub>)<sub>n</sub>; n = 1 or 2; p = 0-2; dashed lines = optional bond(s)]  
 were prepd. Thus, 5-(1-piperazinyl)-1,2,3,4-tetrahydroquinoline was  
 alkylated by Cl(CH<sub>2</sub>)<sub>3</sub>COC<sub>6</sub>H<sub>4</sub>F-4 to give I [Q = (CH<sub>2</sub>)<sub>3</sub>COC<sub>6</sub>H<sub>4</sub>F-4; R-R<sub>4</sub> = H,  
 T = N, Y = Z<sub>1</sub> = Z<sub>2</sub> = CH<sub>2</sub>, dashed lines = null]. Data for biol. activity of

I were given.

**MSTR 1**



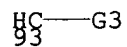
G2 = 12-4 14-5



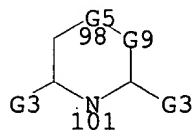
G4 = CH2

G5 = N

G7 = 93



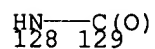
G8 = 98-6 101-95



G9 = (1-2) CH2

G10 = alkyl<(1-3)> (SR Ph)

G11 = 128-112 129-116



G15 = adamantyl (SO (1-) G16)

DER: and salts

MPL: claim 1

BERNHARDT

09/706683

NTE: substitution is restricted

REFERENCE COUNT:

13

REFERENCE(S):

1997

(1) American Home Food Products Inc; EP 0785195 A

CAPLUS

(2) American Home Products; US 5486518 A 1996 CAPLUS

(3) American Home Rproducts; US 5519025 A 1996 CAPLUS

(4) Duphar Int Res; WO 9736893 A 1997 CAPLUS

(5) Duphar International Research; EP 0372657 A 1990

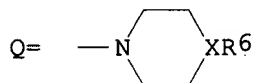
CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 2 MARPAT COPYRIGHT 2001 ACS  
 ACCESSION NUMBER: 120:299317 MARPAT  
 TITLE: Preparation of amino acid amide derivatives as  
 tachykinin antagonists  
 INVENTOR(S): Mase, Toshasu; Kubota, Koichi; Imanishi, Naoki;  
 Tomioka, Kenichi  
 PATENT ASSIGNEE(S): Yamanouchi Pharma Co Ltd, Japan  
 SOURCE: Jpn. Kokai Tokkyo Koho, 32 pp.  
 CODEN: JKXXAF  
 DOCUMENT TYPE: Patent  
 LANGUAGE: Japanese  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05294915	A2	19931109	JP 1992-129510	19920421

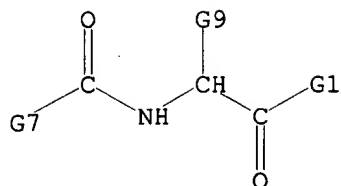
GI



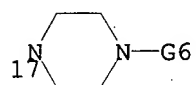
AB Amino acid amide derivs. R3NHCHR4CONR1R2 [R1 = H, lower alkyl, cycloalkyl, aralkyl; R2 = lower alkyl, AR5, NR1R2, Q; A = single bond, linear or branched alkyl alkylene; R5 = (un)substituted Ph or benzhydryl, cycloalkyl; X = N, CH; R6 = H, lower alkyl, Ph, aralkyl; R3 = H, CO2R7, CONHR7, COR8; R7 = lower alkyl, optionally crosslinked cycloalkyl(alkyl), Ph, aralkyl; R8 = R7, (un)substituted fused heterocyclyl; R4 = (un)substituted CH2Ph, benzhydryl, Ph, C3-10 alkyl, cycloalkyl, (un)substituted fused heterocyclylmethyl], optical isomers, or salts thereof, antagonizing tachykinin receptors, particularly substance P, neurokinin A, or neurokinin B receptor, and useful for treating tachykinin-mediated diseases, are prepd. Thus, iso-Bu chloroformate was added to a mixt. of Boc-Phe-OH, N-methylmorpholine, and THF under ice-MeOH

cooling; the mixt. was stirred at at -15.degree. to -20.degree. and reacted with N-methylbenzhydrylamine at room temp. for 2 h to give phenylalaninamide deriv. Boc-Phe-NMeCHPh2 (I). I showed IC50 of 0.58 .mu.M for inhibiting substance P-induced contraction of guinea pig's ileum. A total of 43 I were prepd. Tablet and capsule formulations contg. I were given.

MSTR 1



G1 = 17



G6 = Ph

G7 = 1-adamantyl

G9 = CH<sub>2</sub>Ph (SO)

DER: or salts

MPL: claim 1

STE: or optical isomers